Exemplary transcription factors and related cis elements, the cellular processes impacted, and therapeutic indications include those listed in Figure 5.

Please amend page 10, lines 20-23 to read as follows:

Optimal treatment parameters will vary with the indication, decoy, clinical status, etc., and are generally determined empirically, using guidance provided herein. Several exemplary indications, routes, vehicles or administration, and decoy combinations are disclosed in Figure 6.

Please delete the table on pages 10-11.

In the Drawings:

Please add the enclosed Figures 5 and 6, which correspond to the tables deleted above.

Remarks/Arguments

Specification

The disclosure was objected to because the tables on pages 6-7 and on pages 10-11 were held to be unsuitable for publication as part of the application. The foregoing amendment in the specification, and the submission of the attached new drawings is believed to overcome this objection.

Claim Rejections – 35 U.S.C. § 112

1. Claims 13-27 (all claims pending) were rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made without undue experimentation. United States v. Telectronics, Inc. 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); In re Stephens, 188 USPQ 659

(CCPA 1976). Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue. In re Angstadt, 190 USPQ 214 (CCPA 1976). The mere fact that an extended period of experimentation is necessary does not make such experimentation undue. In re Colianny, 195 USPQ 150 (CCPA 1977). Specific factors which can be considered to determine whether undue experimentation is necessary to practice an invention include (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented in the specification; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

The Rejection

In considering the In re Wands factors, the Examiner heavily relies on (1) the unpredictability of decoy therapy in 1993; (2) the poor correlation between *in vitro* animal models and *in vivo* clinical trial results in patients; and (3) the alleged lack of working examples or other specific teaching in the specification of decoys and techniques for the use of the claimed methods in humans. Specifically, the Examiner notes that as of 1993 decoy therapy was not a tested art "due to the lack of methods or processes for its use in humans." While acknowledging the availability of promising *in vitro* data and results in *in vivo* animal models at the relevant time, the Examiner notes that "*in vitro* and animal models have not correlated well with *in vivo* clinical trials in patients." In addressing the evidence provided by applicants showing the successful use of NFκB decoys for the treatment of ischemic reperfusion injury, inflammatory arthritis, glomerulonephritis, cytokine production an tumor growth in rat animal models, the Examiner notes that applicants presented "no art recognized nexus between the results obtained in rats and the results the skilled artisan would expect to see in humans."

The Disclosure Provides an Enabling Disclosure for the Claimed Invention

The Examiner's reasoning in support of the conclusion that the specification does not provide adequate support for the claimed invention is seriously flawed.

Applicants agree that decoy therapy was a new therapeutic approach in 1993. Indeed, the present invention is of pioneering nature being the first to have experimentally demonstrated the *in vivo* efficacy of the decoy technology in modulating gene transcription via specifically binding to a targeted transcription factor. In other words, the most important contribution of the present inventors has been to demonstrate that *in vitro* test tube observations of transcription factor modification can be transferred to an *in vivo* setting within intact tissues in a living mammal, where a cellular and physiologic effect could be observed. The examples of the specification clearly and without equivocation establish the operability of the invention as an *in vivo* treatment of a living mammal, and the specification teaches both exactly how to use the invention with the specific transcription factors and delivery methods in the examples and exactly how to generalize use of the invention to other transcription factors and other delivery methods well-known in the art.

The Examiner points at *"[s]afety and efficacy issues"* that are "at the forefront of research today in delivery techniques with a continued call for basic research on gene transfer vectors and gene delivery techniques." (Emphasis added.) In addition, the Examiner notes that the "specification does not adequately teach how to effectively prevent or treat NFκB diseases *or reach any therapeutic endpoint in humans*." (Emphasis added.) This reasoning seems to imply that, in the Examiner's view, applicants should have exemplified the workability of the claimed methods in human therapy in order to eliminate the need for undue experimentation. As the Examiner is well aware, the submission of human clinical trial results is not a requirement for patentability of inventions directed to the treatment of humans. It is well known that success in animal models is not a guarantee for successful use in human therapy. Indeed, of many promising drug candidates only a small percentage will make it into a commercial drug product. Many candidates fail along the way for issues of safety, toxicity, bioavailability, efficacy, and the like. However, considering such factors is more properly left for the Food and Drug Administration (FDA) than the Patent Office (Scott v. Finley, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Similarly, review of clinical efficacy at any given therapeutic endpoint is part of the drug approval process, which is the competence of the FDA, and is not the proper legal standard when the patentability of an invention is assessed. Absolute predictability of success in human therapy is not a requirement for patentability, and specifically for

enablement, even if the claimed invention is directed to the treatment of humans. Applicants are required only to provide a reasonable expectation of success, which applicants have done in the present case.

Applicants note that the issues faced when transferring observations from animal models to human clinical use are not in any way unusual or different for the decoy technology utilized in performing the present invention compared to any other new drug candidates. In fact, the Examiner's statement that "in vitro and animal models have not correlated well with in vivo clinical trials in patients" is entirely erroneous with regard to transcription factor decoys. To date, there have been two human clinical trials that have evaluated the efficacy of therapeutic transcription factor decoys, and both have generated positive results – yielding a much higher success rate and much higher degree of predictability than other classes of drugs. Specifically, the safety and biological efficacy of intraoperative gene therapy using an oligonucleotide decoy which binds to and inactivates the pivotal cell-cycle transcription factor E2F was studied in a randomized, controlled human clinical trial (PREVENT). The results of the trial demonstrated that the E2F decoy technology was safe, feasible, and could achieve sequence-specific inhibition of cell-cycle gene expression and DNA replication. For further details see, Mann *et al., Lancet* 354:1493-1498 (1999) (copy enclosed). Another, Phase IIb placebo controlled, double blind, randomized trial investigating the safety and feasibility of treatment of human vein graft failure in coronary artery bypass procedures with the E2F decoy disclosed in the present application was conducted in the Heart Institute in Sieburg, Germany (PREVENT 2). Two hundred patients requiring vein bypass grafts to treat blocked coronary arteries were enrolled in the trial with patients almost evenly divided and randomly assigned to the E2F-decoy treated and the placebo arms. The study showed that a one time, *ex vivo* treatment with E2F decoy was associated with a 30% reduction in a composite index of vein graft failure and death, which was statistically significant. The results from this study were presented in the Late-breaking Clinical Trials Session at the AHA Scientific Sessions in Anaheim, California, November 2001. Although these clinical trials were conducted with E2F decoys, they clearly demonstrate the viability of the decoy technology in the treatment of humans. Indeed, the Examiner cited no reasons why positive results obtained with decoys to one specific transcription factor would not be applicable

to the assessment of the viability of a clinical strategy using similar decoys to another transcription factor.

The Examiner's assertion that "the specification is silent with respect to what decoys and what methods would be utilized to perform this method in humans" is misplaced. The passage cited from page 10, lines 11-19 at page 5 of the Office Action is a general description of suitable methods of administration, but also refers to the "[e]xemplary methods . . . described in the examples." As the Examiner notes, for the introduction of NFκB decoys the table on page 11 identifies polymers and liposomes as suitable delivery vehicles. *In vivo* use of liposomes for delivery of E2F decoys is specifically exemplified in Example 2, and the *in vivo* efficacy of such decoys is demonstrated in Example 3. The preparation of an HVJ-liposome-DNA complex is taught in Example 5, and its *in vivo* use is demonstrated in Example 6. Although these examples are not specific to the delivery and use of NFκB decoys, the Examiner has given no reason why, once the operability of the method is demonstrated with one decoy, one skilled in the art would not expect that decoys targeting other transcription factors could not be delivered and work in a similar way. The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention, and the Examiner has not met this burden.

Indeed, the Examiner's position is in stark contrast with consensus among those skilled in the art. For example, Tomita *et al., J. Am. Soc. Nephrol.* 11:1244-1252 (2000), of record, demonstrate the *in vivo* efficacy of an NFκB decoy in an experimental model of crescentic glomerulonephritis. At page 1244, second column, the authors refer to references (17)-(19) to show that "The decoy approach to blocking transcription factor activity has been shown to be an effective strategy for inhibiting specific gene expression *in vitro* and *in vivo*. While reference (19) concerns the delivery of an NFκB decoy, references (17) and (18) concern the delivery of E2F decoys. Contrary to the Examiner, Tomita *et al.* find that the successful *in vivo* delivery of an E2F decoy is relevant, and has probative value in showing the applicability of the decoy approach to blocking transcription factor activity in general. Similarly, Tomita *et al., Arthritis & Rheumatism* 42:2532-2542 (1999), of record, refers to publications presenting data with E2F decoys to show that the method used for delivery of an NFκB decoy "has been optimized to achieve maximal transfection efficiency." (See page 2533, Column 2.) The method of

preparation of HVJ liposomes described in these publications is essentially the same as that described in Example 2 of the present application. Accordingly, these publications clearly confirm that the method specifically taught in the present application, is suitable for *in vivo* delivery of decoys to block transcription activity in general, and NFκB decoys specifically.

The remaining issue is whether there is sufficient nexus between the *in vivo* animal data, disclosed in the specification or later submitted by applicants, and the results a skilled artisan would expect in humans. "Nexus" requires a factually and legally sufficient connection between the objective evidence provided and the claimed invention, so that the evidence is of probative value in the determination of the issue that it is purported to support. The references of record, which are peer-reviewed papers in reputable scientific journals, themselves provide such nexus. For example, Tomita *et al.* (1999), *supra* states that "the results of this study suggest that, in vivo, direct intraarticular transfection of NFκB decoy ODN provides a new therapeutic approach for the treatment of arthritis." (Page 2533, first column.) Similarly, Sawa *et al.*, *Circulation* 96(Suppl. II); II-280-II-285 (1997), of record, ends with the conclusion that "*in vivo* gene transfection of the *cis* element decoy against NFκB binding site appears to be a novel and future strategy for myocardial protection." The latter statement is also relevant to showing that a person skilled in the art would find that the use of the claimed methods for prevention (protection) is enabled. Indeed, Sawa *et al.* demonstrate that the NFκB decoy provided protection against ischemia reperfusion injury in a rat model, and conclude that this finding is relevant for myocardial protection in general. Quan *et al., FASEB* 15:1616-1618 (2001) (copy enclosed) demonstrated that intravenous injections of an NF-κB decoy inhibits pancreatic activation of NF-κB and prevents diabetogenesis by alloxan in a mouse model. According to the concluding remarks of the paper, ". . . although the results of the present study are obtained in an animal model of chemically induced diabetes, it is likely that the activation of NF-κB also plays a pivotal role in the pathogenesis of human diabetes. In fact, an emerging concept for pathogenesis of numerous degenerative diseases (including diabetes, cancer arthritis, cardiovascular disease, macular degeneration, various neurodegenerative disorders, and aging) is that oxidative stress plays a central role. The present results, therefore, suggest that activation of NF-κB may also be critical for both the pathogenesis and the potential treatment of all of these diseases. Similar statements could be cited from all references of record that present findings in

in vivo animal models, which is not surprising since the *in vivo* animal models are developed with the goal of advancing the development of human therapy. It is, again, emphasized that results of a human clinical trial are not required to overcome the charge of undue experimentation. Positive results obtained with a drug candidate in a recognized animal model have been long recognized by the Patent Office and competent courts as sufficient to support enablement for claims covering the treatment of human subjects.

In view of the present arguments and the totality of evidence of record, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

2. Claims 13-27 were rejected under 35 U.S.C. § 112, first paragraph for alleged lack of adequate written description.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. § 112, first paragraph is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." In re Kaslow, 707 F.2d 1366, 1375, 212 USPQ 1089, 1096 (Fed. Cir. 1983); see also Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See, e.g. Vas-Cath, 935 F.2d at 1563; 19 USPQ2d at 1116. The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Union Oil v. Atlantic Richfield Co., 208 F.3d 989, 996 (Fed. Cir. 2000). In Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), the Federal Circuit held that an adequate written description of genetic material "requires a precise definition, such as by structure, formula, chemical name, or physical properties." A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequences, falling within the scope of the genus or a recitation of structural features to the members of the genus, which features constitute a substantial portion of the genus. *Id.* 119 F.3d at 1569, 43 USPQ2d at 1406. The Guidelines for Examination of Patent Applications Under the

35 U.S.C. § 112, ¶ 1, 'Written Description' Requirement, 66 F.R. 1099, 1106 (January 5, 2001) (hereinafter "Written Description Guidelines") provide that applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Written Description Guidelines at 1106.

The Rejection

The Examiner applies the above-cited standard expressed in *Eli Lilly* and the Written Description Guidelines to conclude that applicants do not provide a written description of an NFκB dsDNA molecule that functions as a decoy to inhibit DNA binding of the NFκB transcription factor. According to the rejection, "decoy molecules with the ability to inhibit NFκB DNA binding must be empirically determined," and that "the disclosed examples are not a representative number of species to show applicants were in possession of the claimed genus."

The Disclosure Provides Sufficient Written Description for the Claimed Invention

The claims pending in the present application concern a method for preventing or treating an NFκB-associated disease or condition in a mammal by introducing an NFκB decoy into a cell of the mammal. Since the claims are not directed to a genus of nucleic acid, *Eli Lilly* is not directly applicable. Indeed, the rule that the disclosure of a sequence is required to provide sufficient written description for a nucleic acid or protein has at least one notable exception. The Revised Interim Written Description Guidelines Training Materials acknowledge that antibodies are structurally well characterized and can be made virtually against all proteins. Accordingly, if a claim is directed to an antibody to a known, well characterized antigen, or to the use of such antibody, the disclosure of the sequence or other structural characteristics of an antibody is not required to comply with the written description requirement of 35 U.S.C. § 112, first paragraph.

As discussed at page 5 of the specification, the decoys used in the methods of the present invention are double-stranded nucleic acid molecules with high binding affinity for the targeted transcription factor, which competitively inhibit binding of the transcription factor to a target gene. Accordingly, the decoys are similar to blocking antibodies in the sense that they bind to a

target protein (transcription factor) and block its ability to modulate transcription of a target gene (e.g. block biological activity of the transcription factor). As discussed at page 8, lines 18-25: "The length, structure and nucleotide sequence of the decoy will vary depending on the targeted transcription factor, the indication, route of administration, etc. For example, targeted transcription factors frequently bind with different degrees of affinity to a variety of sequences, normally sharing a high degree of homology. Accordingly, one may choose to use a sequence associated with a particular target gene or use a consensus sequence based on the nucleotide at each site which occurs most frequently in the binding sequences to which the particular transcription factor binds." According to the teaching at page 8, lines 19-21: "In one embodiment, the decoys are non-replicative oligonucleotides fewer than 100 bp, usually fewer than 50 bp and usually free of coding sequence, being primarily from the non-coding 5' region of a gene."

At the time the present invention was made, NF-κB was well known as a transcription factor (Sen and Baltimore, *Cell* 47:921-928 (1986)), and so were the sequences of its subunits. Thus, for example, the cloning of the human NF-κB p65 DNA binding subunit was reported by Ruben *et al.*, *Science* 251:1490-1493 (1991). It was also known that a variety of genes encoding cytokines, cytokine receptors, cell adhesion molecules, etc. are regulated by NF-κB. NF-κB binding sequences in the promoter regions of various genes regulated by NF-κB were also known. For example, Marois *et al.*, *Mol. Cell. Biol.* 13:6231-40 (1993) reported the characterization of a functional NF-κB site in the human interleukin-1β (IL-1β) promoter. Kunsch and Rosen, *Mol. Cell. Biol.* 13:6137-46 (1993) disclosed the NF-κB transcription factor binding site within the interleukin-8 (IL-8) promoter, and provided evidence of the NF-κB subunit-specific regulation of this promoter. Several groups reported that the NF-κB binding site located between bp –72 and –63 was important for the activation of the IL-6 gene by IL-1, TNF-α or lipopolysaccharide (LPS) (Shimizu *et al.*, *Mol. Cell. Biol.* 10(2):561-568 (1990); Libermann and Baltimore, *Mol. Cell. Biol.* 10:2327-2334 (1990); Zhang *et al.*, *Mol. Cell. Biol.* 10:3818-3813 (1990)).

In view of the general teaching provided in the specification about the design of decoy molecules, the specific example of an E2F decoy, and general knowledge in the art at the time the invention was made (as discussed above), one skilled in the art would have recognized that at

the time the invention was made applicants were in the possession of the invention involving the use of an NFκB decoy.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached pages are captioned "**Version with markings to show changes made.**"

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: December 5, 2003

By: _____

Ginger R. Dreger
Registration No. 33,055
Attorney of Record
Customer No. 20,995
(415) 954-4114

Version with markings to show changes made

In the Specification:

Page 6, lines 6 and 7, has been amended as follows:

Exemplary transcription factors and relate cis elements, the cellular processes impacted and therapeutic indications include[:] those listed in Figure 5.

Page 10, lines 20-23, has been amended as follows:

Optimal treatment parameters will vary with the indication, decoy, clinical status, etc. and are generally determined empirically, using guidance provided herein. Several exemplary indications, routes, [and] vehicles of administration, and decoy combinations are disclosed in Figure 6 [the following table].

The table on pages 6-7 has been deleted.

The table on pages 10-11 has been deleted.

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Figure 5

Cis-element Transcription Factor	Cellular Process	Therapeutic Application
E2F	cell proliferation	neointimal hyperplasia, neoplasia, glomerulonephritis, angiogenesis, inflammation
AP-1	cell growth, differentiation, growth factor expression	neointimal hyperplasia, cardiac myocyte growth/differentiation
NFκB	cytokine expression, leukocyte adhesion molecule expression, oxidant stress response, cAMP and protein kinase C activation, immunoglobulin expression	inflammation, immune response, transplant rejection, ischemia-reperfusion injury, glomerulonephritis
SSRE	response to shear stress: growth factor expression, vasoactive substances, matrix proteins, adhesion molecules	neointimal hyperplasia, bypass grafts, angiogenesis, collateral formation
CREB	cAMP response	cAMP activated events
MEF-2	cardiac myocyte differentiation and hypertrophy	cardiac myocyte growth and differentiation
CArG box	cardiac myocyte differentiation	cardiac myocyte growth and differentiation
tax	viral replication	HTLV infection
VP16	viral replication	Herpes infection
TAR/tat	viral replication	HIV infection
GRE/HRE MRE	glucocorticoid, mineralocorticoid induced events	steroid hormone processes, e.g., breast or prostate cell growth
Heat shock RE	heat shock response	cellular stresses, e.g., ischemia and hypoxia
SRE	growth factor responses	cell proliferation/differentiation
AP-2	cAMP and protein kinase response, retinoic acid response	cell proliferation
sterol response element	modulation of LDL cholesterol receptor expression	hypercholesterolemia
TRE TGFβ responsive element	Transforming growth factor beta-induced cellular processes	cell growth, differentiation, migration, angiogenesis, intimal hyperplasia, matrix generation, apoptosis

FIGURE 6

INDICATION	ROUTE	VEHICLE	PLASMD/ OLIGONUCLEOTIDE
HIV infection	Intravenous injection	gp160 in neutral liposomes	TAR containing oligonucleotide
Solid tumor	Intratumoral injection	Tumor-specific Antibody with liposomes	E2F
Inflammatory skin diseases and dermatitis	Topical	Polymer	NFκB, E2F
Hypercholesterolemia	Intravenous injection Portal vein injection	Cationic liposomes asialoglycoprotein receptor targeting with liposomes	Sterol responsive element to increase LDL receptors
Vein bypass grafts	Topical/intraluminal	Polymer, liposomes	E2F
Glomerulonephritis	Intravenous, intrarenal	Polymer, liposomes	E2F, NFκB
Myocardial infarction	Intracoronary	Liposomes, polymer	NFκB, E2F, AP-1
Organ transplant e.g., cardiac/renal	Intravascular, ex vivo	Liposomes, polymer	NFκB